VOLUME 1 of 7

PETITION FOR TOLERANCE

Bacillus thuringiensis subsp. *tolworthi* Cry9C Protein
in or on the Raw Agricultural Commodity, Corn

April 19, 2001

SUBMITTED BY:

Luann Powell
Registration Manager, Regulatory Affairs – Biotechnology

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ON BEHALF OF THE APPLICANT:

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STATEMENT OF **NO** CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10(d) (1) (A), (B), (C).

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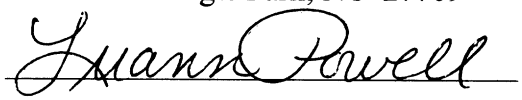
Company Agent: 

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Date : April 18, 2001

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Branch Chief: Phil Hutton
cc: Michael Mendelsohn

April 19, 2001

Subject: **Petition for the establishment of tolerance for *Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein in or on the raw agricultural commodity, corn**

Re: **EPA Registration Number 264-669 (cancelled)**

Dear Mr. Hutton:

Pursuant to section 408 of the Federal Food, Drug, and Cosmetic Act, Aventis CropScience USA LP (Aventis) respectfully submits a petition for tolerance of 20 parts per billion (20 ppb) for *Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein in or on the raw agricultural commodity, corn. The 20-ppb tolerance would be conditioned upon the requirement that all lots of raw corn delivered for dry milling be subject to testing by an approved Lateral Flow Strip Test.

As you are aware, an exemption from the tolerance requirement is in effect for Cry9C protein in feed and an amended petition is pending PPF5050 for an exemption for a four-year period for the protein in food.

As a result of the detection of Cry9C-related DNA in food items, in September 2000, Aventis announced that it would not market StarLink™ corn in the year 2001. Furthermore, in October 2000, Aventis voluntarily cancelled its registration for StarLink corn.

Since the November 2000 FIFRA Scientific Advisory Panel (SAP) meeting, Aventis, grain handlers, and the milling industries have developed methods and performed studies to address questions by the SAP. In addition, Aventis, grain handlers, the milling industry, and many others have made tremendous efforts to identify and properly channel StarLink corn and other Cry9C protein containing corn to animal feed and industrial non-food uses.

The enclosed updated exposure assessment was prepared to account for the Cry9C-containing corn that may have entered the food chain from the 1999 and 2000 growing seasons. This assessment draws on more accurate data than previously existed, in that actual Cry9C protein values from representative milled processed foods have now been generated. These more accurate values allow for a more refined dietary exposure assessment.

This exposure assessment (Volume 2) is based on the following recently completed studies and reports:

- Detection of Cry9C Protein in Dry-milled, Wet-milled and Masa Processed Fractions and Processed Foods Made From 100% StarLink™ Grain (Volume 5). This study demonstrates the dramatic reduction in Cry9C protein levels that results when raw commodities are processed into finished foods; and

- StarLink™ Corn Containment Program Report. This report describes Aventis' efforts to prevent Cry9C protein from entering the human food supply (Volume 6).

In addition, the following materials are being submitted:

- Development of ELISA Assay to Detect Cry9C-Specific IgG and IgE Antibodies in Human Serum (Volume 3);

- Aventis Position on Follow Up with Individuals Alleging Allergic Reactions to Corn Ingestion (Letter from Aventis to Administrator Whitman, Secretary Veneman, and Dr. Schwetz) (Volume 4); and

- The Aventis CropScience StarLink™ Quality √ Plan for corn dry mills (Volume7).

Attached to this transmittal letter is an executive summary that provides an overview of the newly submitted data and describes the factual and legal bases for the petition.

A check for the tolerance fee ($68,000.00) has been sent to the EPA Headquarters Accounting Operations Branch in Pittsburgh, PA.

If you have any questions or would like clarification on this submission, please do not hesitate to contact me at (919) 549-2748.

Sincerely,

Luann Powell

Luann Powell
Registration Manager, Regulatory Affairs –Biotechnology

Enclosures (3 copies of Volumes 1-7)

Volume #	FIFRA Data Requirement	Title Correct titles	MRID#
1	Not Applicable	Administrative Materials	
2	Not Applicable	Estimated Potential Dietary Intake Of Cry9C Protein Based On Measurements Of Cry9C In Processed Foods Made From 100% StarLink™ Corn	
3	Not Applicable	Development of ELISA Assays to Detect Cry9C-Specific IgG and IgE Antibodies in Human Serum	
4	Not Applicable	Aventis Position on Follow Up with Individuals Alleging Allergic Reactions to Corn Ingestion (Letter from Aventis to Administrator Whitman, Secretary Veneman, and Dr. Schwetz)	N/A
5	Not Applicable	Detection of Cry9C Protein In Dry Milled, Wet Milled and Masa Processed Fractions and Processed Foods Made From 100% StarLink™ Grain	
6	Not Applicable	StarLink Corn Containment Program	
7	Not Applicable	The Aventis CropScience StarLink™ Quality √ Plan for Corn Dry Mills	

Petition for Tolerance for *Bacillus thuringiensis* subsp. *tolworthi* Cry9C Protein in or on the Raw Agricultural Commodity, Corn

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SECTION A: NAME, CHEMICAL IDENTITY, AND COMPOSITION

A petition for tolerance at 20 ppb is proposed for *Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein in or on the raw agricultural commodity, corn.

The following studies provide data for Cry9C protein. These studies were submitted and reviewed in support of the application for registration of StarLink corn product, EPA Reg. No. 264-669.

Product Chemistry – Molecular Characterization	
MRID # 44384403	Expanded molecular characterization of the corn transformation event CBH351

Product Chemistry – Biochemical Characterization	
MRID # 44258103	Characterization of Cry9C and PAT protein levels in corn under field conditions [Annex 1: In-Field Characterization] [Annex 2: Genotype Characterization]

SECTION B: THE AMOUNT, FREQUENCY, AND TIME OF APPLICATION OF THE PESTICIDAL CHEMICAL

In October 2000, Aventis voluntarily cancelled its EPA registration for Cry9C, StarLink™ corn. Although the registration is cancelled, the most current version of the label is included in this petition.

The residues in question resulted from use of the product, the label of which is attached.

StarLink™ CORN

StarLink™ corn produces both an insecticidal protein, Cry9C from *Bacillus thuringiensis* subsp. *tolworthi,* for protection from European corn borer and Southwestern corn borer, suppression of Black cut worm and Common stalk borer, and a herbicide resistance protein, phosphinothricin acetyltransferase (PAT). PAT provides protection from the Liberty® herbicide (EPA Registration Number 264-660), a herbicide that has glufosinate-ammonium as its active ingredient.

StarLink™ corn are descended from corn plants transformed with vectors pRVA9909 and pDE110.

KEEP OUT OF REACH OF CHILDREN

CAUTION

Active Ingredient:	*Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein and the genetic material necessary for its production in corn	0.9-4.7%†*
Inert Ingredients:	Substance produced by a marker gene and its controlling sequences in corn	0.2-1.6%†

† The percentages list the ingredient as a percent of the total plant protein on a dry weight basis.
* US Patents pending.

EPA Registration No. **264-669**
EPA Establishment Number: **070218-BEL-001**

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling. Keep out of lakes, ponds or streams. Do not contaminate water by cleaning of equipment or disposal of wastes. All field corn containing the plant-pesticide that is sold or distributed by Aventis CropScience USA LP or a cooperator or licensee of Aventis, must be accompanied by informational material that contains the following:

StarLink™ corn contain a *Bacillus thuringiensis* subsp. *tolworthi* insecticidal protein, Cry9C and may only be used according to the instructions below for the control of the following insects:

European corn borer	*Ostrinia nubilalis* (Huber)
Southwestern corn borer	*Diatraea grandiosella* (Dyar)

StarLink™ corn contain a *Bacillus thuringiensis* subsp. *tolworthi* insecticidal protein, Cry9C and may only be used according to the instructions below for the suppression of the following insects:

Black cut worm	*Agrotis ipsion* (Hufnagel)
Common stalk borer	*Papaipema nebris* (Guen.)

Do not use this corn until you have read the Bag Tag and the Grower's Guide.

Insect Resistant Management: To protect this important technology, a structured non-*Bt* corn refuge must be planted in close proximity to your StarLink™ corn fields. Specifically, a structured refuge of non-*Bt* corn equal to at least 20% of the total corn acres must be planted. The refuge must be located within ½ mile of the StarLink™ field, unless you plan to use a foliar-applied insecticide for Corn borer control; then it must be planted within ¼ mile. Any insecticide treatment for Corn borer cannot include sprayable Bt products.

Seed Production Uses: Seeds expressing the Cry9C protein should be planted at a maximum of 40,000 seeds per acre on the site. Any seeds, plants or plant materials in the StarLink™ field, or within 660 feet of the field that is not used for seed production should be destroyed or used domestically for animal feed or non-food industrial purposes. None of the seeds, plants or plant materials in the StarLink™ field, or within 660 feet of the field, may be used for food uses or may enter international commerce.

Feed or Non-food Industrial Uses: Seeds expressing the Cry9C protein should be planted at a maximum of 40,000 seeds per acre on the site. Any seeds, plants or plant materials in the StarLink™ field, or within 660 feet of the field, should be used domestically for animal feed or non-food industrial purposes. None of the seeds, plants or plant materials in the StarLink™ plot, or within 660 feet of the field, may be used for food uses or may enter international commerce.

STORAGE AND DISPOSAL

Seed Storage: Store in a cool dry place separate from conventional corn seed.

Seed and Plant Disposal: Any seeds, plants or plant materials in the StarLink™ field, or within 660 feet of the field, may be used domestically for animal feed or industrial purposes, or destroyed. None of the seeds, plants or plant materials in the StarLink™ field, or within 660 feet of the field, may be used for food uses or may enter international commerce.

Container Disposal: Do not reuse bag. Discard bag in trash. Ensure that the bag is completely empty of seed before disposal.

For Product Inquiry Information,
Call Toll Free: 1-877-STARLINK
(1-877-782-7546)

The registration of this pesticide product for use in field corn will automatically expire on midnight April 1, 2001. After this registration has expired, no field corn seed that contain the pesticide product may be sold or planted. However, harvesting of the corn planted prior April 1, 2001 is permissible subject to the terms of this registration.

SECTION C: FULL REPORTS OF INVESTIGATION MADE WITH RESPECT TO SAFETY

The following studies evaluate the mammalian toxicology of the Cry9C protein. The Agency has already determined that there is no toxicity associated with Cry9C protein except for an open question regarding allergenicity.

Some of these studies have been previously submitted and reviewed in support of the application for registration of StarLink™ corn product, EPA Reg. No. 264-669. This submission contains a new dietary exposure assessment (Volume 2) based on new residue data which demonstrates the levels of Cry9C protein in intermediate and finished food products as well as the results of the efforts to contain the Cry9C containing corn. In addition, this section includes a report on methodology for detecting Cry9C specific antibodies in blood serum (Volume 3) and also a paper which provides a scientifically defined pathway for investigating individuals that alleged reactions following consumption of corn products (Volume 4).

Volume No.	Study Title	EPA MRID#
	An acute oral toxicity study in mice with Cry9C protein as purified from *Bacillus thuringiensis* Cry9C.PGS2	44258107
	In vitro digestibility and heat stability of the endotoxin Cry9C protein sequence	44258108
	Amino acid sequence homology search with the corn expressed truncated Cry9C protein sequences	44258109
	Cry9C *Bt* insecticidal protein Identification of sequence homology with allergens by searching protein databanks	44384404
	Investigation of allergens in wild-type and transgenic corn	44394405
	Safety assessment of StarLink™ corn, genetically modified corn containing the truncated *Bt* insecticidal protein Cry9C, for human food use	44714001
	Bt Cry9C protein: Investigative study of the potential for binding to mouse intestinal brush membrane vesicles	44734301
	Bt Cry9C protein mouse acute intravenous toxicity study	44734302
	Mouse short-term (30 day) dietary toxicity study with the protein Cry9C	44734303
	Phosphinothricin Acetyltranferase and Cry9C protein content in processed fractions of transgenic field corn event CBH351	45025701

	Development of New Methods for Safety Evaluation of Transgenic Food Crops	44714002
	Occupational Exposure of StarLink™ Corn: Garst Seeds, 1996-1998	44714003
	Assessment of the stability to digestion and bioavailability of the LYS mutant Cry9C protein from *Bacillus thuringiensis* serovar *tolworthi*	44734305
	The effect of corn hybrid CBH351 on the growth of male broiler chickens	44734036
	The digestibility of the Cry9C protein by simulated gastric fluids and intestinal fluids	45114401
	Comparison of the *In Vitro* Digestibility based upon pH of the Endotoxin Cry9C derived from *Escherichia coli* and *Bacillus thuringiensis*	45114402
	Evaluation of IgE AntiBody Reactivity of Food Allergic Subjects of StarLink Corn	45246401
	Revised, Updated Safety Assessment of StarLink Corn Containing Cry9C Protein	45256701
	Cry9C Protein content in grain of transgenic field corn event CBH351	45260302
	ELISA Analysis of Cry9C protein in CBH351 StarLink Corn subject to pilot scale Alkaline processing	452735301
	ELISA and Western Blot Analysis of Cry9C protein present in StarLink Corn samples obtained via pilot scale Alkaline processing	45275302
	Analysis of Taco Shells for Cry9C Protein	45246402
	Preliminary Study for Detection of CBH351 DNA in Taco Shells: (Investigations carried out between afternoon of 9/22/00 – morning of 9/28/00)	45240201
	Further Studies on Detection of CBH351DNA in Taco Shells: (Investigations carried out between afternoon of 9/28/00 – morning of 9/29/00)	45240202
	Preliminary Study for Detection of Cry9C Protein in Taco Shells	45240203

2 of 7	ESTIMATED POTENTIAL DIETARY INTAKE OF CRY9C PROTEIN BASED ON MEASUREMENTS OF CRY9C IN PROCESSED FOODS MADE FORM 100% STARLINK™ CORN	
3 of 7	Development of ELISA assays to Detect Cry9C-Specific IgG and IgE Antibodies in Human Serum	
4 of 7	Aventis Position on Follow Up with Individuals Alleging Allergenic Reactions to Corn Ingestion; Letter to Administrator Whitman, Secretary Veneman and Dr. Schwetz	

SECTION D: THE RESULTS OF TESTS ON THE AMOUNT OF RESIDUE REMAINING, INCLUDING A DESCRIPTION OF THE ANALYTICAL METHOD USED

Studies regarding residues of Cry9C protein that support this petition are listed below.

Some of these studies were previously submitted and reviewed in support of the application for registration of the StarLink™ corn product, EPA Reg. No. 264-669.

This submission contains a study report from the investigation of new Cry9C protein residue data in intermediate and finished food products made from 100% StarLink corn (Volume 3).

Volume No.	Study Title	EPA MRID#
	Characterization of Cry9C and PAT protein levels in corn under field conditions [Annex 1: In-Field Characterization] [Annex 2: Genotype Characterization]	44258103
	ELISA Analysis of Cry9C protein in CBH351 StarLink Corn subject to pilot scale Alkaline processing	45275301
	ELISA and Western Blot Analysis of Cry9C protein present in StarLink Corn samples obtained via pilot scale Alkaline processing	45275302
	Analysis of Taco Shells for Cry9C Protein	45246401
	Preliminary Study for Detection of CBH351 DNA in Taco Shells: (Investigations carried out between afternoon of 9/22/00 -- morning of 9/28/00)	45240201
	Further Studies on Detection of CBH351DNA in Taco Shells: (Investigations carried out between afternoon of 9/22/00 -- morning of 9/28/00)	45240202
	Preliminary Study for Detection of Cry9C Protein in Taco Shells	45240203
	Cry9C Protein content in grain of transgenic field corn event CBH351, USA, 1998	45260302

5 of 7	Detection of Cry9C protein in dry milled, wet milled and masa processed fractions and processed foods made from 100% StarLink™ grain	

SECTION E: PRACTICABLE METHODS FOR REMOVING RESIDUE THAT EXCEEDS ANY PROPOSED TOLERANCES

The two programs listed below have been developed to limit the residue to a maximum of 20 ppb.

In addition, the proposed tolerance would be conditioned on screening of all inbound corn shipments to dry millers.

Volume No.	Study Title	EPA MRID#
6 of 7	StarLink Corn Containment Program	
7 of 7	The Aventis CropScience StarLink™ Quality √ Plan for Corn Dry Mills	

SECTION F: PROPOSED TOLERANCE

An exemption from tolerance for Cry9C protein and the genetic material necessary for the production of this protein already is in effect for corn used for feed and non-food industrial uses. This current petition proposes a tolerance at the level of 20 ppb for the raw agricultural commodity, corn, used to make human food. This proposed tolerance is conditioned on the testing of corn delivered to dry mills using a lateral flow strip test that has been approved by the Grain Inspection, Packers, and Stockyards Administration (GIPSA) and Aventis with a level of detection of 20 ppb.

SECTION G: REASONABLE GROUNDS IN SUPPORT OF THE PETITION

Reasonable grounds to support this petition for tolerance for *Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein in or on all the raw agricultural commodity, corn are presented in the following section.

I. EXECUTIVE SUMMARY

In this submission, Aventis CropScience ("Aventis") (1) addresses important issues raised in the December 2000 report by EPA's Scientific Advisory Panel ("SAP") about possible consumer exposure to StarLink™ corn, (2) submits the results of studies undertaken to resolve these issues, and (3) urges EPA to establish a tolerance at the level of 20 ppb Cry9C protein coupled with mandatory screening of corn inbound to the mills. This tolerance will assure that any human dietary exposure to Cry9C protein remains insignificant.

As fully documented in this submission, newly available data establish that the tolerance would be safe and that EPA has ample authority to grant the proposed tolerance. The proposed tolerance is fully consistent with the judgments expressed by the SAP in December. It also would avoid major disruptions to the food supply, provide regulatory certainty, restore consumer confidence, and help preserve vital export markets.

In 1998 and the two following years, EPA approved the registration of StarLink corn for animal feed and non-food industrial applications. This "split registration" was based on the assumption that crops produced for such uses could be completely segregated from the human food supply. It is now clear that assumption was incorrect, as EPA recently acknowledged by announcing that it will no longer grant split registrations for products of biotechnology. The grain handlers, food industry, and Aventis have undertaken extraordinary measures to prevent corn containing Cry9C protein from entering the food supply. In spite of

these efforts, trace levels of Cry9C protein will continue to be unavoidably present in grain. Moreover, it is now understood that it was inevitable that the commercial introduction of StarLink corn for feed use would cause the introduction of Cry9C protein into the general grain supply because of the biology of corn, gene flow, and the processes used in handling grain. It is therefore necessary to establish a tolerance to provide a clear and protective legal standard for unforeseen and unavoidable levels of Cry9C protein found in the human food supply. Trace levels of Cry9C protein in human food pose no safety concern but will present continuing and intractable regulatory issues in the absence of an appropriate tolerance.

The studies and analyses that Aventis is now submitting show that exposure to Cry9C protein is well below the worst case exposure levels previously assumed by EPA and the SAP. The exposure continues to decline and poses no significant risk. Trace levels of Cry9C protein are likely to continue to appear for the foreseeable future in some food made from domestic yellow corn. This is due to dispersal of stocks of StarLink corn already present in grain handling channels, the existence of other varieties of corn that contain some level of Cry9C protein, volunteer corn, and corn residues in grain handling, transportation, and storage equipment. The anomalous result is that, so long as the government views any level of Cry9C protein, detected by any method of analysis, as rendering food legally adulterated, major disruptions of the food supply will continue even though the theoretical risk is vanishingly small. This outcome would not contribute to the protection of public health or represent wise public policy.

Aventis proposes a resolution of the current untenable situation that, first and foremost, fully protects consumers and, simultaneously, provides a clear standard for enforcement of the adulteration provisions of the Federal Food, Drug, and Cosmetic Act

("FDCA"). Aventis proposes that EPA establish a finite tolerance for Cry9C protein for raw corn, conditioned on prescribed testing. Specifically, Aventis proposes a tolerance of 20 parts per billion (ppb) for Cry9C protein, conditioned on a requirement that all lots of raw corn delivered for dry milling be subject to Lateral Flow Strip testing ("strip testing") at a limit of detection of 20 ppb. All lots of corn that test positive by this method would, as now, be diverted to animal feed or non-food industrial uses.

Adoption of this proposal would fully protect consumers even if suggestions that Cry9C protein might be an allergen remain unresolved. Further, it would minimize disruptive recalls of food that poses no public health concern. Adoption of this proposal would be consistent with the requirements and the pertinent history of the Food Quality Protection Act ("FQPA"). Under section 408 of the FDCA, as rewritten by the FQPA, EPA must find that the tolerance is "safe," which the statute defines as "reasonable certainty of no harm." The long history of this legal standard in the FDCA confirms that this is not a zero-risk standard. It does not require EPA to find that all potential exposure has been eliminated.

This proposal also is consistent with the judgments expressed in the SAP report in December 2000 and supported by the new information submitted here and by the ongoing efforts to identify, control, and prevent human consumption of corn containing Cry9C protein.

The situation that EPA now confronts differs from that considered by the SAP four months ago in several important respects:

1. The grain handlers, milling industry, Aventis, and many others have made aggressive efforts, described below, to identify and contain StarLink corn and to direct it to appropriate non-food uses. As demonstrated in Volume 6, measures already taken will minimize any Cry9C protein in the 2001 corn crop; other measures have effectively confined and diverted

almost all of the StarLink corn grown in 2000; and most of the remaining StarLink corn from the 1999 harvest has been captured and is being properly channeled to approved uses. Pursuant to Food and Drug Administration (FDA) guidance and with Aventis support, dry millers are actively screening incoming shipments of corn and diverting lots that test positive to animal feed or non-food industrial uses.

2. EPA has concluded that the DNA of plant-incorporated protectants is safe. EPA is expected to publish a final rule granting a tolerance exemption for the DNA of plant-incorporated protectants. The issuance of that rule is vital to the resolution of the Cry9C problem. The regulatory focus should, then shift to regulating the Cry9C protein.

3. EPA has published a white paper (now open for public comment) concluding that food fractions produced by wet milling contain virtually no Cry9C protein. EPA also concluded that there is no likely health concern associated with the consumption of any food fraction produced by wet milling, even including corn starch that might contain up to 16 ppb Cry9C protein. These findings thus confine any concerns about the possible allergenic effects of Cry9C protein to the much smaller universe of foods made from dry milled corn.

4. Since the SAP meeting, Aventis has worked with strip test manufacturers to develop a more accurate, reliable, and easy-to-use strip test. To date, Aventis has distributed more than 1.7 million strip tests to elevators and millers.

5. Aventis has developed reliable, validated methods for extracting and detecting Cry9C protein in processed foods. Aventis also has studied the factors affecting Cry9C protein breakdown during food processing. These studies confirm that, with the proposed mandatory testing of raw corn inbound to the mills, no detectable levels of Cry9C protein would

be present in cereals, snack foods and masa-derived products. Other dry-milled food products would contain, at most, extremely low levels of Cry9C protein.

6. Aventis has made extensive contacts within the scientific and academic communities as well as federal regulatory agencies to determine what additional research could be undertaken to study the allergenic potential of Cry9C protein. The conclusion was that there are no existing validated test protocols or models to further prove that Cry9C protein is not an allergen. For assistance in evaluating individuals alleging allergic reactions to Cry9C protein, Aventis has commissioned an independent laboratory that has developed an ELISA test method for Cry9C protein-specific antibodies in blood. To determine background levels, this methodology was used to analyze blood samples collected before and after the commercialization of StarLink.

7. New exposure analyses have taken account of the amount of corn containing Cry9C protein that may have entered the food supply, the effects of processing on Cry9C protein, and the consumption of corn products by different subgroups within the U.S. population. The studies show that worst case exposure levels for Cry9C protein in processed food are an order of magnitude lower than the exposure levels assumed by the SAP and EPA in the fall of 2000, and confirm that any risk associated with Cry9C protein exposure would be negligible.

The studies being submitted with this document, coupled with the measures already taken by the grain handlers, the milling industry, Aventis, and others to identify and divert StarLink corn, now enable the quantification of actual levels of Cry9C protein that could possibly be found in processed foods. This quantification provides strong reassurance that any

possible dietary risk to consumers is extremely low. This finding is consistent with, and indeed was anticipated by, the SAP's December 1, 2000, report.

The proposed tolerance with required screening at dry mills would be more protective of human health than the exemption previously proposed in that it would cap the amount of Cry9C protein that potentially could reach the human food supply. At the same time, the proposed tolerance would resolve the uncertainty that now exists concerning the legal status of food products containing trace amounts of Cry9C protein and avert pointless disruption in food markets.

The proposal also meets EPA's (and FDA's) need for a lawful and enforceable solution. The strip test has been widely used and is capable of detecting any Cry9C protein in corn that might be of public health concern. It is economical, reliable, and familiar to grain handlers, corn millers, and agency personnel. Establishment of a finite tolerance at 20 ppb would provide a clear legal standard for regulatory authorities as well as corn grain suppliers and food processors in the United States and important export markets.

This submission provides the factual data and legal basis to support EPA's establishment of a 20 ppb tolerance for Cry9C protein conditioned on mandatory strip testing of raw corn inbound to mills. This is a legal and readily enforceable solution to an otherwise intractable problem. The Cry9C protein that remains in, or which might conceivably reach, the human food supply poses no significant risk to human health. That notwithstanding, if EPA does not act now, the ongoing disruption in the domestic and international food markets -- in the form of recalls and rejections of exported products -- undoubtedly will escalate.

II. COMPONENTS OF THE SUBMISSION

This section has three components.

The first is a brief historical summary of StarLink regulation, the discovery of *cry9C* DNA in taco shells in September 2000, and Aventis' extensive and continuing efforts to contain StarLink corn.

The second part describes in detail the new reports that address the SAP requests:

- The StarLink corn containment report describes Aventis' efforts to prevent Cry9C protein from entering the human food supply.
- The Quality √ Plan describes the mandatory screening on which the proposed tolerance would be conditioned and the procedures for documenting compliance with the mandatory screening.
- The protein study demonstrates the dramatic reduction in Cry9C protein levels that results when raw commodities are processed into finished foods.
- The updated exposure assessment prepared by Novigen Sciences, Inc., builds on the corn containment report and protein study and estimates the maximum potential dietary exposure to Cry9C protein. The current estimates are based on very conservative assumptions and are likely to be overstated. Nevertheless, they show that the potential human dietary exposure is a fraction of the "extremely low" exposure levels calculated by Novigen in November 2000.
- The report on the method for detecting Cry9C-specific protein antibodies in blood provides the mechanism to determine whether an individual has been exposed to Cry9C protein. In addition, the documents include the recommendation made to FDA for follow up with individuals claiming allergic reactions to ingestion of corn-containing products.

Taken together, these reports demonstrate that a tolerance of 20 ppb in raw agricultural commodity, corn is safe.

The third part explains that, based on these scientific reports and analytical data, EPA has the legal authority to establish a tolerance at the 20 ppb level.

III. REGULATORY AND FACTUAL BACKGROUND OF STARLINK CORN

Plant Genetic Systems (America) ("PGS"), a predecessor of Aventis, developed a transgenic line of corn plants containing an insect control protein, Cry9C, that is derived from the common soil bacterium *Bacillus thuringiensis* subsp. *tolworthi.* The Cry9C protein is effective in combating the European corn borer, a lepidopteran pest. Licensed corn hybrids expressing Cry9C protein are referred to by the trade name StarLink.

A. Initial Registration of StarLink and Exemption from a Tolerance for Cry9C Residues

On April 4, 1997, PGS submitted an application to EPA to register Cry9C protein and the genetic material necessary for the production of the protein ("*cry9C* DNA") under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"). That application requested that Cry9C protein and *cry9C* DNA be registered for use in or on the raw agricultural commodity, corn. Concurrent with its registration application, PGS petitioned EPA for an exemption from the requirement for a tolerance for Cry9C protein and *cry9C* DNA.

On May 12, 1998, EPA issued a registration for StarLink corn that limited its use to animal feed, and non-food industrial applications. This "split registration" was granted by EPA while further data were developed to assess the potential allergenicity of the Cry9C protein. It was based on the assumption that crops produced for animal feed and non-food industrial uses could be completely segregated from the human food supply. This assumption proved unrealistic, as EPA acknowledged when it announced, on March 7, 2001, that it no longer would grant split registrations for products of biotechnology.[1]

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[1] *See EPA Releases Draft Report on Starlink Corn* (March 7, 2001), *available at* http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/cd9013801973259885256a0800710574.

Soon after the split registration was granted, EPA published in the Federal Register an exemption from a tolerance for Cry9C protein and *cry9C* DNA residues "only in corn used for feed; as well as in meat, poultry, milk, or eggs resulting from animals fed such feed."[2]

B. Petition for an Exemption from a Tolerance for Cry9C Protein Residues in Human Food

In October 1998, the registration for Cry9C protein and its associated DNA was transferred from PGS to AgrEvo USA Company ("AgrEvo"), the successor to PGS and a predecessor of Aventis. The following month, AgrEvo submitted a new petition seeking to extend the exemption from a tolerance to all agricultural corn uses. On April 7, 1999, EPA published in the Federal Register a notice announcing the filing of this petition[3] and seeking comment on the potential allergenicity of the Cry9C protein.[4] EPA raised this issue because Cry9C protein is digested more slowly than other marketed Cry proteins, which have not been found to be allergens.

In February 2000, the first StarLink-specific SAP considered whether the Cry9C protein might be a human allergen. (By this time, Aventis had been formed by the merger of AgrEvo and Rhone-Poulenc Ag Company, and Aventis had assumed the FIFRA registration for StarLink corn.) In June 2000, the SAP issued a report of that meeting, which noted that, "based

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2 63 Fed. Reg. 28258 (May 22, 1998).

3 64 Fed. Reg. 16965 (April 7, 1999).

4 64 Fed. Reg. 71452 (December 21, 1999).

on the available data, there is no evidence to indicate that Cry9C is or is not a potential food allergen."[5]

C. Detection of Cry9C in the Human Food Supply and Aventis' Response

In September 2000 *cry9C* DNA was detected in taco shells. In response, Aventis promptly halted all sales of StarLink seed and voluntarily requested revocation of the FIFRA registration for Cry9C protein and *cry9C* DNA in StarLink corn. EPA subsequently revoked the registration.[6]

Beginning on September 29, 2000, Aventis, in conjunction with the United States Department of Agriculture (USDA), also took aggressive steps to locate and direct all StarLink and buffer corn to approved uses. Aventis launched the StarLink Enhanced Stewardship Program to contain StarLink corn and other corn containing Cry9C protein from the 2000 crop on-farm and ensure the channeling of all such corn to approved animal feed and non-food industrial uses. The attached StarLink "Corn Containment Program" Report (Volume 6) describes these efforts, which include the following:

- Aventis has supplied over 1.7 million test strips to grain elevator operators to help them identify corn containing Cry9C protein, thus enabling the industry to divert corn testing positive for Cry9C protein at or above 20 ppb to approved animal feed and non-food industrial uses.
- Separately, wet and dry millers have implemented inbound testing to ensure that they do not receive corn containing Cry9C protein. Any corn testing positive for Cry9C is diverted to approved feed and non-food industrial uses.

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[5] SAP Report No. 2000-01A, *FIFRA Scientific Advisory Panel Meeting, February 29, 2000, Session I - A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Food Allergenicity of Cry9C Endotoxin and Other Non-digestible Proteins*, page 8 (June 29, 2000).

[6] 66 Fed. Reg. 4825 (January 18, 2001).

- To ensure that Cry9C protein at levels greater than 20 ppb will not enter the food supply through "new sources": (i) programs are in place to identify and destroy existing StarLink seed inventory, (ii) programs are in place to provide information and advice to growers with respect to the handling of volunteer corn, and (iii) Aventis has ceased all field trials and development of StarLink corn.

- Aventis has established a claims procedure for costs incurred in diverting corn testing positive for Cry9C protein to animal feed and non-food industrial uses. A precondition for processing these claims is documentation of delivery to approved uses. Accordingly, all participants in the corn-growing and corn-processing chain have an incentive to divert and document the diversion of corn that tests positive for the presence of Cry9C protein.

Aventis has taken these actions although it believes that Cry9C protein does not present a human dietary risk.

D. Petition for a Time-Limited Tolerance Exemption for Cry9C Residues in Human Food

On October 25, 2000, Aventis submitted an addendum to its November 1998 petition for a food tolerance exemption, seeking a time-limited exemption for Cry9C protein in food. This petition focused on Cry9C protein because EPA had already indicated that DNA is not known to cause adverse health effects when consumed as part of food, a position that was confirmed in the not-yet-promulgated Plant-Incorporated Protectant Rule.[7] Aventis requested a four-year exemption, which was the time estimated for Cry9C protein to work its way through the channels of trade.

The October 2000 addendum included a human safety assessment of Cry9C prepared on behalf of Aventis by Novigen. This report evaluated the maximum potential human

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[7] Exemption from the Requirement of a Tolerance under the Federal Food, Drug, and Cosmetic Act for Residues of Nucleic Acids that are Part of Plant-Incorporated Protectants (formerly Plant-Pesticides), *available at* http://www.epa.gov/scipoly/6057-5.pdf.

dietary exposure to Cry9C protein in food products and therefore presented a worst-case scenario. Following discussions with EPA, Aventis submitted revised and updated Novigen assessments in November 2000 which utilized methodology consistent with that used by EPA to estimate dietary exposure to pesticide residues.

E. Responses by EPA and the FIFRA Scientific Advisory Panel

EPA issued a preliminary evaluation of Aventis' initial assessment on November 13, 2000. In its evaluation, the Agency noted: "EPA thinks that the available information supports an overall conclusion that the potential dietary exposure to the Cry9C protein is extremely low…."[8] At the same time, EPA determined that existing evidence was insufficient to determine whether the Cry9C protein is a human allergen. EPA did conclude, however, that "the DNA necessary for the production of Cry9C lacks the potential to cause allergic reactions."[9]

EPA prepared this preliminary evaluation for a meeting of the SAP on November 28, 2000. The December 1, 2000, report of this meeting concluded that there is a "medium" likelihood that Cry9C is a potential allergen, but that the levels of Cry9C protein entering the human diet presented a "low" likelihood of sensitizing individuals even if the protein is an allergen, as well as a "low" likelihood of eliciting an allergic reaction in sensitized individuals. The SAP recommended that the following data be obtained to improve the scientific basis for assessing the potential for Cry9C protein to elicit allergic reactions:

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[8] EPA Preliminary Evaluation of Information Contained in the October 25, 2000 Submission from Aventis CropScience, page 2, *available at* http://www.epa.gov/scipoly/sap/2000/november/prelim_eval_sub102500.pdf.

[9] *Id*. at page 7. Despite this finding, the Agency has not yet issued the pending Plant-Incorporated Protectant rule establishing a general exemption for residues of nucleic acids produced in living plants as a result of plant-pesticide activity.

- Data on the levels of Cry9C protein in processed food. The SAP noted that there was a need for validated analytical methods to test for Cry9C protein in processed foods.

- Data on the impact of processing methods on Cry9C levels in processed foods. The SAP noted that "[d]ata indicating that Cry9C is reduced or eliminated during processing would obviously support a conclusion of a low dietary risk from StarLink corn."

- Data on the extent of mixing of StarLink corn with corn that does not contain Cry9C protein.

Reports appended to the present submission address each of these requests.

The SAP also requested data on the presence of antibodies in individuals who claim to have had adverse reactions following consumption of corn products. Aventis is aware that such studies are being undertaken by FDA and the Centers for Disease Control. Aventis has submitted a letter to EPA, FDA, and USDA offering suggestions with respect to protocols for these tests (Volume 4). Aventis also furnished to FDA the test methods for Cry9C-specific antibody detection on human blood (Volume 3).

IV. NEW DATA ASSEMBLED BY AVENTIS ADDRESS SPECIFIC ISSUES RAISED BY THE SAP AND DEMONSTRATE THAT THE POTENTIAL FOR HUMAN DIETARY EXPOSURE TO CRY9C PROTEIN IS NEGLIGIBLE

This submission provides new scientific and analytical data concerning the potential for human dietary exposure to Cry9C protein. The new exposure assessment shows that the level of Cry9C protein in the food supply is substantially lower than that assumed by the SAP in the fall and is continuing to decrease. Accordingly, what presented a "low" likelihood of causing allergic reactions in November-December of 2000 presents a lower likelihood today, and a diminishingly lower likelihood in the future. However, current information suggests that trace levels (parts per billion) of Cry9C protein are likely to continue for some time to appear occasionally in food made from domestic yellow corn.

To put the new findings in context, we summarize briefly the findings of the previous exposure assessments by Aventis, EPA, and the SAP and the assumptions on which those findings were based.

A. The Original Exposure Assessment and the Concerns Raised By the SAP

The original exposure assessment performed by Novigen for Aventis was based on several assumptions, including:

- 0.0129% of all crude protein in StarLink corn is Cry9C protein and that 0.4% of all corn grain in the U.S. in 2000 is StarLink corn.
- All Cry9C protein in dry-milled products passes through to processed products and is not reduced by processing or cooking.
- The original assessment did not take into account the potential for Cry9C protein exposure from wet-milled products. Since the date of that assessment, EPA's own assessment of the impact of wet milling has shown that there is virtually no exposure to Cry9C from wet milled products.

Based on these assumptions, Novigen estimated that the subpopulation with the highest consumption evaluated (99th percentile) of products containing corn protein (the Hispanic population) could consume 3.9 micrograms of Cry9C protein per day in 2000.

EPA's preliminary evaluation of the original exposure assessment (November 13, 2000) noted that there was insufficient information from which to determine whether Cry9C protein is a human allergen but went on to conclude that the potential for dietary exposure to Cry9C protein was "extremely low." Following a review of the data submitted by Aventis, the SAP concluded that there is a "medium" likelihood that Cry9C is a potential allergen. The SAP advised that the possible levels of Cry9C protein in the human diet presented a "low" likelihood

of sensitizing individuals to the protein even if Cry9C protein were an allergen[10] and that lowering the levels of Cry9C in the food supply would make sensitization even less likely.[11] Finally, the SAP concluded that there was a "low" likelihood that the levels of Cry9C assumed at that time to be present in the human diet were sufficient to cause allergic reactions in the exposed population. Thus, the SAP linked lower exposure to lower human allergenic risk.

The SAP also requested data concerning the impact of food processing and cooking on Cry9C protein as well as a validated method for detecting Cry9C protein in processed food. The SAP noted that "data indicating that Cry9C is generally not detectable in processed food or that Cry9C is present at extremely low levels would support the assessment of a low dietary risk from StarLink™ corn."

B. New Materials

Aventis undertook three activities to respond to exposure-related questions raised by the SAP.

- The report titled "StarLink Corn Containment Program" (the "containment report") describes the extensive efforts of Aventis, growers, elevator operators, millers, and USDA to direct StarLink corn grown during the 1999 and 2000 growing seasons to approved non-food uses.

- The study titled "**Error! Bookmark not defined.**" (the "protein study") was undertaken to determine whether and to what extent Cry9C protein present in food made from 100% StarLink corn is reduced or eliminated by food processing methods. Aventis also responded to the SAP request that Aventis develop validated analytical methods for detecting Cry9C protein in processed food. (EPA already has released its own evaluation of wet-milled products, reported in the "white paper" discussed below.)

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[10] SAP Report No. 2000-06, *FIFRA Scientific Advisory Panel Meeting, November 28, 2000, A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Assessment of Scientific Information Concerning StarLink Corn*,™ pages 10, 13 (December 1, 2000).

[11] *Id*., page 24.

- The study titled "Estimated Potential Dietary Intake of Cry9C Protein Based on Measurements of Cry9C in Processed Foods Made from 100% StarLink™ Corn" (the "updated exposure assessment") built on the results of the containment report and protein study in assessing the potential for human dietary exposure, if any, to Cry9C protein.

The findings of these investigations are summarized below. Taken together, they compel the following conclusions. First, the potential for human dietary exposure to Cry9C protein has been reduced to miniscule levels by two factors: (i) the containment efforts undertaken by Aventis, growers, elevator operators, millers, and USDA, and (ii) commercial and home food processing methods, which reduce Cry9C protein in raw commodities by 80% to greater than 99.9%. Taking these findings into account, the updated exposure assessment shows that the potential for human dietary exposure to Cry9C protein is a tiny fraction of the level that EPA and the SAP found presented a "low" risk of sensitization and allergic reaction. Even though the risk to consumer health is miniscule and continuing to decrease, the presence of trace levels of Cry9C protein in corn products cannot be wholly eliminated.

1. Wet Milling White Paper

EPA's wet milling white paper noted that wet milled products "intended for human food consumption contain no or extremely low levels of intact protein."[12] This finding confirms an assumption of Aventis' November 2000 exposure assessment.

Wet-milled products are used for animal feed, non-food industrial uses, and human food. The four wet-milled products used for human food are corn oil, alcohol (ethanol), corn syrup, and corn starch. EPA found that Cry9C protein is not present in corn oil, alcohol, or

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[12] EPA White Paper on the Possible Presence of Cry9C Protein in Processed Human Foods Made from Food Fractions Produced through the Wet Milling of Corn, page 2.

in corn syrup, but may be present at extremely low levels in corn starch. EPA assumed that the amount of Cry9C protein that might be present in corn starch is 16 nanograms per gram, which is equivalent to 16 ppb. Based on that assumption, EPA estimated the "upper bound" of the potential daily exposure to Cry9C protein in corn starch for consumers in the 99th percentile in the year 2000 at 0.013 micrograms. EPA noted that these exposure numbers "are given in micrograms in order to emphasize the extremely low amounts of Cry9C protein that might be present."[13] EPA concluded:

> EPA believes it is reasonable to conclude that there is virtually no Cry9C protein in wet milled products and that *there is no likely health concern for the public associated with the consumption of any food fraction produced by wet milling of corn* as long as reasonable steps are taken to ensure that StarLink corn is not diverted to wet milling. Data show that corn protein will not be present in high fructose corn syrup, corn oil, or alcohol (ethanol). Data also indicate that corn starch will contain, at most, such extremely low levels of corn protein that there is virtually no potential human exposure to Cry9C protein from consumption of corn starch.[14]

EPA's emphasis on the extremely low levels of potential human dietary exposure from corn starch and the absence of any public health concern arising out of this potential exposure means that potential exposure to Cry9C protein due to ingestion of dry-milled products is the sole focus of possible concern. New data provided by Aventis demonstrate that the potential exposure, if any, from dry-milled corn is likewise minimal and does not present a public health concern.

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13 *Id*., page 13.

14 *Id*., page 14 (emphasis added).

2. StarLink Corn Containment Program Report

The containment report describes the extensive efforts made by Aventis, grain handlers, corn millers, and others to contain all StarLink corn grown in the United States and to direct Cry9C-containing corn to approved non-food uses.[15] StarLink was grown commercially during the 1999 and 2000 growing seasons. Of the approximately 80 million acres planted with corn in the United States each year, the StarLink fields accounted for approximately 250,000 acres (0.3% of the total) in 1999 and approximately 350,000 in 2000 (0.4% of the total). As soon as *cry9C* DNA was discovered in taco shells during the fall of 2000, Aventis took steps to contain StarLink corn that already had been grown, StarLink corn commingled with conventional corn, as well as corn containing some percentage of Cry9C protein to direct Cry9C-containing corn to approved non-food uses. These efforts have been very successful. For a variety of reasons, however, it is not possible to contain all of this corn. Therefore some small, albeit diminishing, level of Cry9C protein is likely to be present in the corn supply for the foreseeable future.

2000 Crop. The vast majority of the corn grown from StarLink seed during 2000 was captured before it left the farm. Of the approximately 49.1 million bushels of StarLink corn grown in 2000, only 30,000 bushels (0.06% of the total), which had left the farm before September 29, 2000, remain unaccounted for. Thus, well over 99% of the corn grown from StarLink seed during 2000 has been diverted or is in the process of being diverted to animal feed or non-food industrial uses and will not enter the human food supply.

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[15] Aventis provides weekly updates on this program to USDA. This petition incorporates data from April 10, 2001.

In addition to the StarLink crop, Aventis has identified approximately 50 million bushels of non-StarLink grain (most from neighboring "buffer corn" and other corn varieties discovered to contain Cry9C) that have lower levels of Cry9C protein than corn grown directly from StarLink seed. According to EPA requirements, non-StarLink corn was grown as a 660-foot buffer surrounding and adjacent to StarLink corn in order to trap StarLink corn pollen. Furthermore, refuges of non-StarLink corn utilized for insect resistance management purposes (20% of total StarLink corn acreage) also could have been pollinated with StarLink corn pollen due to pollen drift. All this corn has been contained and, to date, about half of this corn has been fed on farm or moved to USDA approved locations.

Aventis also has contacted its seed licensees and advised them to destroy their stocks of 2000 StarLink seed and to ensure that seed sold in 2001 is strip tested for Cry9C protein. The major seed producers, USDA, and Aventis have agreed to pay for the destruction of seed corn that tests positive for Cry9C. Thus, it is likely no new corn seed containing significant amounts of Cry9C will be sold in the future. However, it is likely that there will continue to be sources of low levels of Cry9C in seed containing undetectable levels of Cry9C protein, in volunteer corn from 2000 StarLink fields or buffer zones, and in Cry9C-containing grain residue in equipment. To ensure that any corn containing 20 ppb Cry9C protein, which is found in 2001 and beyond does not reach the food supply, Aventis and the dry milling industry have put in place a voluntary testing program by which each incoming load of grain is strip tested. All corn testing positive at or above 20 ppb Cry9C protein is diverted to animal feed or non-food

industrial uses. Thus, current programs ensure that corn that reaches the human food supply will contain no or exceedingly low levels of Cry9C protein.[16]

1999 Crop. There is incomplete knowledge about the disposition of the approximately 37.5 million bushels of StarLink corn grown in 1999, before the containment efforts described above had been put in place. It is likely that the majority of the 1999 crop did not enter the human food chain because less than 20% of the total corn crop is used for food and because the registration for StarLink limited its use to animal feed and non-food industrial uses. Nevertheless, some small amount of StarLink clearly did enter the human food supply where it became commingled with and diluted by a much larger volume of conventional corn. About 437 million bushels of commingled corn have been identified. Aventis is working with grain elevator operators to ensure that this corn is used solely for animal feed and non-food industrial uses. To date, 94 million bushels (22%) have been diverted to animal feed or non-food industrial uses.

By the end of 2000, seventy percent of the United States 1999 corn crop had been processed. The strip testing described above will help to prevent additional commingled corn containing 20 ppb or above Cry9C protein from entering the human food supply for processing. The potential for human exposure to Cry9C protein from StarLink corn that already is in the human food supply will be reduced by two factors: (i) dilution by commingling with a large volume of non-Cry9C containing corn, and (ii) processing methods, as discussed in the Aventis protein study summarized below.

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[16] The report is appended as Volume 6.

3. StarLink Quality √ Plan for Corn Dry Mills

Aventis has developed a program to restrict the movement of Cry9C protein into foods produced from dry milled corn. This program, the StarLink Quality √ Plan, specifies the testing of corn from each container arriving at mills, utilizing the lateral flow strip test capable of detecting Cry9C protein at 20 ppb or above. The Quality √ Plan Protocol describes the corn dry-milling industry and how corn is received and processed in dry mills. It then discusses the two types of tests that are available to detect the presence of Cry9C protein. A mill may receive 200-600 trucks per day, each containing up to 900 bushels of corn. Only the lateral flow strip test is fast and practical enough to be used at the point of corn receipt at the mill.

The Quality √ Protocols include directions for the following: (a) representative sampling of shipments of corn grain; (b) administration of the lateral flow strip test; (c) procedures for recording test results; and (d) validation of testing procedures. Shipments testing positive for Cry9C protein will be directed to approved non-food uses. As part of the Quality √ Program, Aventis also will make available to participating mills a quality assurance program to monitor compliance with the protocols mentioned above. Finally, Aventis will offer training to ensure that program participants are able to comply with the plan in a consistent and accurate manner.

4. Protein Study

The protein study addresses the SAP's request for data concerning the impact of food processing by analyzing the effect of wet milling, dry milling, and masa processing on Cry9C protein. This study tested processed foods that were made from 100% StarLink grain to provide a worst-case assessment of the amount of Cry9C protein residues that might remain after

processing. It demonstrates that processing substantially reduces -- from 80% to greater than 99.9% -- the amount of Cry9C protein in finished food products.

Twelve representative corn-containing foods were prepared and tested. The dramatic loss of Cry9C protein in these finished food products resulted from recipe dilution (the addition of ingredients other than corn) and processing methods. All processing methods reduce the amount of Cry9C protein significantly because they involve heat, shear or pressure, and/or alkali treatment. The degree of the reduction depends on the specific processing method used. The greater the dilution and the more harsh the processing, the lower the level of the Cry9C protein in the finished food product. The foods tested were produced by small-scale rather then larger-scale commercial processing. The smaller-scale processing may underrepresent the reduction in Cry9C protein from larger-scale commercial processing.

The study also validated the Envirologix Enzyme Linked ImmunoSorbent Assay ("ELISA") test for use in connection with the 12 foods tested. This assay (the "plate test") was able to detect Cry9C protein present at 0.35 parts per billion in food ingredients or finished products. Unlike the lateral flow strip test, the plate test is time consuming and requires controlled laboratory conditions. It is not suitable for use in the field, because it requires specialized equipment and trained professionals.

Various product groups were tested for Cry9C protein using the plate test: wet-milled, masa processed, and dry-milled. The data indicate that, for all products, food processing causes a dramatic reduction in Cry9C protein levels in the finished food when compared to the raw corn from which the finished food is made.

The absolute values reflected in this study demonstrate the impact of processing on Cry9C protein levels. These levels are not likely to occur in foods made commercially from available corn stocks.

Wet milling. The testing showed that wet-milled production of starch from 100% StarLink corn led to the loss of more than 99.9% of the Cry9C protein and no Cry9C protein was detected in the refined oil. These findings are consistent with EPA's wet milling white paper.

Masa processing. Finished foods produced by the masa process also contained extremely low levels of Cry9C protein. Cry9C protein was detected, at 23.6 and 20.3 ppb, in only two of the six different samples tested. The amount of Cry9C protein was below the detection limit in the remaining samples.

Dry milling. Barely quantifiable levels of the Cry9C protein were found in corn snacks and cereal corn products produced using the degermed corn meal fraction of 100% StarLink grain. The highest Cry9C protein levels were detected in cooked polenta, corn bread, corn muffins, and hush puppies. The uncooked mixes for these products undoubtedly would have higher levels of Cry9C protein. However, even in these products, processing substantially reduced the amount of Cry9C protein; 14% for corn bread, 70% for polenta, 71% for corn muffins, and 64% for hush puppies. The updated exposure assessment discussed below considered the impact of processing on foods made with raw corn that did not exceed the 20 ppb Cry9C protein threshold from testing at the entry point to the mill.

5. Updated Exposure Assessment

The updated exposure assessment[17] (Volume 2) estimates the potential for dietary exposure to Cry9C protein resulting from human intake of all processed foods that might contain some percentage of corn protein. At the 99th percentile, the US population potentially would consume 0.37 micrograms of Cry9C protein per day. No particular U.S. subpopulation examined has greater potential exposure than the U.S. population at large. The overwhelming majority (95%) of the U.S. population potentially would consume no more than 0.1 microgram per day and three-quarters would consume no detectable levels or none at all. These figures are extremely conservative, but they are more than ten times lower than the highest estimates Aventis provided to the SAP in November 2000 (3.9 micrograms per day for the Hispanic population at the 99th percentile).[18]

The updated exposure assessment yields figures that are 80-95% less than those provided by Aventis to the SAP in November 2000. The updated exposure assessment yields exposure estimates that are 97.7 to 99.4% less than those provided by the EPA to the SAP last fall. Both the Aventis November and the updated assessments are extremely conservative with the result that the analysis almost certainly overstates the potential for exposure to Cry9C

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[17] Barbara J. Petersen, Ph.D., Nancy J. Rachman, Ph.D., and Joanne L. Watters, Novigen Sciences, Inc., Estimated Potential Dietary Intake of Cry9C Protein Based on Measurements of Cry9C in Processed Foods Made from 100% StarLink™ Corn (April 12, 2001).

[18] The November 2000 assessment showed that the subpopulation believed to be most highly exposed was the Hispanic population. This was based on the comparatively high consumption of foods containing corn protein by this subpopulation. The updated exposure assessment shows that no age group or ethnic subpopulation examined is more exposed than the U.S. population as a whole. This is because the updated exposure assessment took into account the fact that the corn-containing foods consumed by the Hispanic population are produced primarily by masa processing, which substantially reduces Cry9C protein in the finished food.

protein. The chart that follows provides a comparison of the results of the updated and previous exposure estimates.

Comparison of Estimated Dietary
Exposure to Cry 9C Protein (99th Percentile)

	Aventis 2000[19]	EPA 2000[20]	Aventis 2001	% Reduction Aventis 2001-2000	% Reduction Aventis 2001 to EPA 2000
US Population	3	25	0.37	88.0	98.5
US Population 1 - 6 years of age	1.5	11	0.25	83.3	97.7
US Population 7 - 12 years of age	2.4	17	0.24	90.0	98.6
Hispanic Population	3.9	33	0.21	94.6	99.4
Hispanic Population 1 - 6 years of age	1.7	--[21]	0.15	91.2	-
Hispanic Population 7 - 12 years of age	2.7	--[21]	0.14	94.8	-

The key differences from the original exposure estimates are provided by the containment and protein studies. Under the containment program, raw corn that tests positive for Cry9C protein using a strip test sensitive to 20 ppb (equivalent to 0.125% or one kernel StarLink

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[19] Aventis Revised Updated Safety Assessment of StarLink Corn Containing Cry9C Protein, page 34-35.

[20] EPA Preliminary Evaluation of Information Contained in the October 26, 2000 Submission from Aventis CropScience, at page 21 (Table 9, Estimated Upper Bound Exposure for Various Population Groups for 2000 Assuming Food Containing Corn Protein was Made from Grain Containing 1.5% StarLink Corn).

[21] Not statistically reliable above 95th percentile.

corn in an 800-kernel sample) is being diverted to animal feed or non-food industrial uses. The exposure assessment assumes that the entire U.S. corn supply contains 0.125% (or 20 ppb) of Cry9C protein. In fact, if the maximum is 20 ppb, then the average is almost certainly significantly less than 20 ppb.

The updated exposure assessment also incorporates the very substantial processing reductions demonstrated by the protein study. The tested products represented 90% of human consumption of food containing corn protein in the United States. The updated exposure assessment took into account 100% of the corn product consumption in the United States. It did so by assigning conservative default values to Cry9C protein. Where the protein study found that Cry9C was not detectable after processing, the updated exposure assessment assigned a Cry9C protein value equal to the limit of detection of the Envirologix ELISA test or 0.35 ppb. For food products that were not represented by the products tested in the protein study, the updated exposure assessment assigned Cry9C protein values equal to those found in corn meal and corn flour, which are the corn products with the highest Cry9C protein residues, without allowing for any reduction by processing. In addition, the exposure assessment took corn starch consumption into account despite EPA's comment that there is "virtually no potential human exposure to Cry9C protein from consumption of food starch."

6. Summary

The new data submitted here indicate that screening and processing will minimize the potential for consumers to be exposed to any significant amounts of Cry9C protein. Even if all corn used for food contains 20 ppb Cry9C protein and even if Cry9C protein is an allergen, the highest consumers of corn products will not encounter enough Cry9C protein to experience either sensitization or allergic reaction.

That said, the same data also indicate that the occurrence of Cry9C protein in the food supply is not likely to be wholly eliminated for the foreseeable future. Small amounts of Cry9C protein are widely dispersed, albeit at low levels, throughout the corn supply. Although those levels are likely to diminish over time, it is clear that residues of Cry9C protein will persist in the human food supply for an indeterminate period.

V. OTHER RESPONSES BY AVENTIS TO ADDRESS ADDITIONAL SAP RECOMMENDATIONS

1. Report on the Method for Detecting Cry9C Antibodies in Blood

Aventis developed a test method to determine whether humans have been exposed to Cry9C protein and, if so, whether they have developed specific antibodies to the Cry9C protein. The validation of the method included determining background levels of reactivity of people not exposed to StarLink corn. This was accomplished by analyzing both pre- and post-1998 blood samples. Aventis has provided this methodology to FDA to facilitate FDA's evaluation of serum samples from individuals claiming to have had a reaction following consumption of corn products.

2. Recommendation to FDA for Testing Strategies for Cry9C Allergenicity

Use of an antibody test such as the one Aventis developed is a necessary first step to determine whether individuals are allergic to Cry9C protein, but it is not enough to prove allergenicity. Aventis has recommended to FDA a testing protocol to facilitate FDA's efforts to confirm or negate the hypothesis that Cry9C protein might be a human allergen. This protocol describes three types of testing: antibody studies, skin prick tests, and Double Blind Placebo Controlled Food Challenge (DBPCFC). As described above, Aventis has developed an ELISA test to detect the presence of antibodies to Cry9C protein.

3. Low Exposure Reduces Risk of Allergenicity

It is not known whether Cry9C protein is a human food allergen. However, it is well established that the process of becoming allergic to any food "requires multiple exposures over a period of time at sufficient levels to become sensitized."[22] Once "sensitized," the experience of an adverse allergic response ("elicitation") requires re-exposure to that protein. It also has long been known that the level of exposure needed to induce antibody formation against a protein (i.e., to "sensitize") is much higher than the level of exposure needed to produce an adverse allergic reaction. Put simply, if one accepts the unproven premise that Cry9C protein is an allergen, the potentially allergic individual is less likely to be sensitized if he or she is exposed only to miniscule amounts of Cry9C protein. The lower the exposure is, the fewer the individuals who will be likely to show any reaction. The updated exposure assessment demonstrates that the potential for dietary exposure is minimal.

VI. EPA HAS AUTHORITY UNDER THE FOOD, DRUG, AND COSMETIC ACT (FDCA) TO ADOPT THE PROPOSED TOLERANCE

Section 408 of the FDCA gives EPA ample authority to establish a tolerance at the 20 ppb level for Cry9C protein with the required screening proposed by Aventis. Under 408(a), EPA must find that any tolerance is "safe," a standard that is defined by the statute to mean "a reasonable certainty of no harm" from aggregate exposure to residues of the pesticide. This standard, which Congress transplanted from section 409 of the FDCA, consistently has been interpreted to mean a finding, based on an appropriate analysis of risk, that a substance poses no more than a negligible or insignificant risk to human health. The statute thus does not impose a

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[22] Communication to the FIFRA Scientific Advisory Panel of October 20, 2000, from Steve L. Taylor, Professor and co-director of the Food Allergy Research and Resource Program at the University of Nebraska, October 13, 2000.

zero-risk standard. The statute also gives EPA authority to condition a tolerance on the use of specified screening or detection methods. That is precisely what Aventis proposes.

Aventis currently has pending before EPA a petition for an exemption from the requirement for a tolerance for Cry9C protein residues. Given the advances in detection technology and newly developed information about the actual levels of potential human dietary exposure to Cry9C protein, Aventis now believes it is feasible and appropriate to request a more limited agency action in the form of a finite, reliably enforceable tolerance rather than an exemption.

A. The FQPA Gives EPA the Authority to Establish Tolerances for Pesticide Residues in Food Based on a Determination that the Tolerance Provides a Reasonable Certainty of No Harm

Under section 408 of the FDCA, a pesticide chemical residue in or on food is deemed "unsafe" (and therefore renders the food "adulterated" under section 402 of the statute) unless (a) a tolerance is in effect and the residue is within the tolerance, or (b) an exemption from the requirement of a tolerance is in effect.[23] Under what is known as the "pass-through" provision, residues in a processed food are permitted provided (a) they have been removed to the extent possible in good manufacturing practice, and (b) they do not exceed the tolerance for the raw agricultural commodity from which the processed food is made.[24] If, on the other hand, a residue "concentrates" in finished food, it requires a separate tolerance.

EPA may establish a tolerance if it determines that the tolerance is safe. "Safe" means that EPA has determined "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures

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23 Section 408(a)(1) of the FDCA. *See also* section 408(a)(4) of the FDCA.

24 Section 408(a)(2) of the FDCA.

and all other exposures for which there is reliable information."[25] In setting a tolerance, EPA is instructed to consider several factors, prominently including "available information concerning the dietary consumption patterns of consumers."[26] When considering consumer exposure, EPA may consider available data and information on the anticipated levels of the pesticide in food and the actual -- rather than theoretical or worst case -- residue levels measured in food.[27]

B. The FQPA Eliminated the Delaney Clause "Zero Risk" Standard and Replaced it with a Uniform Science-Based Health Standard

Before the passage of the FQPA, EPA regulated pesticide residues that concentrated in food as food additives under section 409 of the FDCA. Section 409 includes a Delaney Clause, which flatly prohibits the use of a carcinogenic food additive at any level even if it is judged to pose only a negligible risk. EPA attempted to avoid this result by recognizing a *de minimis* exception to the Delaney Clause.[28] The Ninth Circuit rejected this approach and stated unequivocally that the law imposed a zero-risk standard.[29] When Congress subsequently passed the FQPA, one of its main goals was to eliminate the Delaney zero-risk standard for pesticide residues on food. As amended by the FQPA, section 408 of the FDCA accordingly subjects all pesticide tolerances to a non-zero science-based safety standard. Section 408 authorizes EPA to set a tolerance for a pesticide residue on raw or processed food if it finds that the tolerance presents a "reasonable certainty of no harm." This standard, which authorizes the exercise of scientific judgment, has a long history in the FDCA.

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25 Section 408(b)(2)(A)(i) and (ii) of the FDCA.

26 Section 408(b)(2)(D)(iv) of the FDCA.

27 Section 408(b)(2)(F) of the FDCA.

28 53 Fed. Reg. 41104 (October 19, 1988).

29 *Les* v. *Reilly*, 968 F. 2d 985 (9th Cir. 1992).

C. FDA has Interpreted the "Reasonable Certainty of No Harm" Standard as a Showing of Negligible or Insignificant Risk Based on a Risk Assessment

The "reasonable certainty of no harm" standard originated with the Food Additives Amendment of 1958 (which added section 409 of the FDCA). In the FQPA, Congress incorporated this "safety" standard into section 408 with the express intention that EPA would continue to exercise scientific judgment in assessing pesticide risks and with the clear understanding that the adopted standard does not mandate zero risk.

The legislative history of the Food Additives Amendment makes clear that "safe" does not mean zero risk. The 1958 House Report stated:

> The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstance.
>
> This was emphasized particularly by the scientific panel which testified before the subcommittee. The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance. . . .
>
> Thus, the safety of a given additive involves informed judgments based on educated estimates by scientists and experts of the anticipated ingestion of an additive by man and animals under likely patterns of use.
>
> Reasonable certainty determined in this fashion that an additive will be safe, will protect the public health from harm and will permit sound progress in food technology.[30]

The 1958 Senate Report concurred, noting that "the test which should determine whether or not a particular additive may be in a specific percentage or relationship to the volume

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[30] H.R. Rep. No. 2284, 85th Cong., 2d Sess. 825-826 (July 28, 1958)

of the product to which it might be added should be that of reasonable certainty in the minds of competent scientists that the additive is not harmful to man or animal."[31] FDA adopted these exact concepts in its food additive regulations, which still define "safe" or "safety" to mean "there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance."[32]

FDA's application of the section 409 "safe" standard always has been founded on an explicit recognition of the relationship between the quantity of a substance consumed and the effect of that substance on human health. When establishing procedures for manufacturers to notify FDA of a determination that a substance added to food is "generally recognized as safe" (or "GRAS") and therefore is not a food additive, FDA affirmed that:

> the common scientific principle "the dose makes the poison," underlies a determination that a substance is safe for use in food at certain levels even if it exhibits toxicity when present at higher levels. A related scientific principle is that the toxicity of a substance may vary between animal species. FDA relies on both of these scientific principles when determining whether the proposed use of a substance added to food is safe within the meaning of section 409 of the [FDCA].[33]

The magnitude of dietary exposure to a substance is a key element in determining safety under section 409. For this reason, the scientific evidence required to obtain approval for a food additive may "vary considerably depending upon the estimated dietary exposure to the

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31 S. Rep. No. 2422, 85th Cong., 2d Sess. 914-915 (August 18, 1958).

32 21 CFR 170.3(i).

33 62 Fed. Reg. 18937, 18942 (April 17, 1997).

substance and the chemical, physical, and physiological properties of the substance."[34] In some cases, FDA has recognized, "dietary exposure is unlikely to present a basis for a safety concern."[35] FDA has determined that human exposure to some substances in food is so low that it can be judged "safe" under section 409 without the need for extensive toxicological testing or formal risk assessment. In 1995, FDA adopted a "threshold of regulation" policy under which food contact substances, and their constituents, are exempt from regulation as food additives if any migration to food will not result in dietary concentrations in excess of 0.5 ppb.[36] As calculated by FDA, this is equivalent to consumption of 1.5 micrograms per person per day.[37] This policy exempts such substances from regulation as food additives and from normal testing requirements. It is therefore tantamount to a finding that noncarcinogenic substances that could get into food at levels of 0.5 ppb or less can be considered safe based on exposure alone.

In sum, FDA has interpreted the "reasonable certainty of no harm" standard that now appears in the FQPA as a negligible or insignificant risk standard, not a zero risk standard. In assessing risk under this standard, FDA has placed great -- if not dispositive -- weight on the magnitude of exposure to the substance in question.

D. Other Health Protection Laws Incorporate an Insignificant Risk Standard.

Other health protection laws require government agencies to make a determination that a substance or activity is safe for humans. Such laws have not been interpreted to require that regulation completely eliminate all risk. Most notably, in setting aside

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34 62 Fed. Reg. at 18942.

35 62 Fed. Reg. at 18943.

36 21 CFR 170.39.

37 *Id*.

the standard set by the Occupational Safety and Health Administration for workplace exposure to benzene, the U.S. Supreme Court declared: "'safe' is not the equivalent of 'risk free.' . . .a workplace can hardly be considered 'unsafe' unless it threatens the workers with a significant risk of harm." The Court added "Congress was concerned, not with absolute safety, but with the elimination of significant harm."[38] Chief Justice Burger concurred: "Inherent in this statutory scheme is authority to refrain from regulation of insignificant or de minimis risk. . . .Perfect safety is a chimera; regulation must not strangle human activity in the search for the impossible."[39]

The Court came to a similar conclusion earlier this year when it held that EPA could not consider costs of compliance when setting ambient air quality standards under the Clean Air Act. Justice Breyer, concurring with the majority, wrote: "After all, the EPA, in setting standards that 'protect the public health' with 'an adequate margin of safety,' retains discretionary authority to avoid regulating risks that it reasonably concludes are trivial in context."[40] He added that the statutory language "does not describe a world that is free of all risk -- an impossible and undesirable objective."[41]

E. EPA Has Used a Negligible Risk Standard in Setting Pesticide Tolerances

When Congress enacted the FQPA, it indicated that the science-based approach to evaluating risks that FDA and EPA had followed under section 409 should apply to tolerance

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38 *Industrial Union Dept., AFL-CIO* v. *American Petroleum Institute*, 448 U.S. 607, 642, 646 (1980).

39 *Id*. at 664-665.

40 *Whitman* v. *American Trucking Ass'ns*, 121 S. Ct. 903, *924 (2001).

41 *Id*. at * 923.

determinations under section 408. The House Report commented that it expected EPA to continue its current risk assessment practices for both threshold and nonthreshold substances:

> The Committee has adopted the standard of "reasonable certainty of no harm" based on EPA's current application of the standard. The Committee understands that the Administrator currently applies this standard differently to threshold and nonthreshold effects. . . .
>
> In the case of a threshold effect for a pesticide chemical residue, the Committee expects that a tolerance will provide a "reasonably certainty of no harm" if the Administrator determines that the aggregate exposure to the pesticide chemical residue will be lower by an ample margin of safety than the level at which the pesticide chemical residue will not cause or contribute to any known or anticipated harm to human health. The Committee further expects, based on discussions with the Environmental Protection Agency, that the Administrator will interpret an ample margin of safety to be a 100-fold safety factor applied to the scientifically determined "no observable effect" level when data are extrapolated from animal studies.
>
> In the case of a nonthreshold effect which can be assessed through quantitative risk assessment, such as a cancer effect, the Committee expects, based on its understanding of current EPA practice, that a tolerance will be considered to provide a "reasonable certainty of no harm" if any increase in lifetime risk, based on quantitative risk assessment, using conservative assumptions, will be no greater than "negligible."[42]

These threshold and nonthreshold risk assessment examples illustrate the approaches that Congress expected EPA to follow in evaluating the most common data sets it confronts. They do not, however, exhaust the universe of analyses that may justify a conclusion that exposure to a pesticide is safe. As the National Research Council commented in a study

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[42] H.R. Rep. 104-669, Part 2 at 40-41.

commissioned by Congress to review the methods that EPA uses to assess toxicological risk, "Risk assessment is not a single, fixed mode of analysis."[43]

Possible allergens do not fit squarely within either of the examples quoted in the House Report. But that does not preclude EPA from evaluating substances that display a different safety profile. Congress expected that EPA would refine or adopt the existing risk assessment analyses or develop new ones as the need arose. This in fact is what EPA and FDA have done for decades.

Simply put, EPA's responsibility is to arrive at the best judgment that the available scientific data allows. Both members of Congress and the Agency itself said precisely that during the consideration of the FQPA. The comments of senators at that time indicated that, by removing pesticide residues from the ambit of the inflexible Delaney Clause, Congress intended to authorize EPA to exercise its scientific judgment, not to abdicate it. Senator Pryor noted that the Delaney Clause "became obsolete with the advances in science and technology."[44] EPA also confirmed that its mission was to use contemporary scientific judgment. [45]

The safety standard in section 408 of the FDCA not only permits but requires EPA to exercise scientific judgment. As far back as 1958, Congress observed "the safety of a given additive involves informed judgments based on educated estimates [of exposure] by

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43 National Research Council, *Science and Judgment in Risk Assessment*, at 4 (1994).

44 142 Cong. Rec. S 8736, S 8738 (July 24, 1996) (Statement of Senator Pryor).

45 Letter from Lynn R. Goldman, M.D., Assistant Administrator, United States EPA, to Hon. Thomas Bliley, Chairman, Committee on Commerce, United States House of Representatives (July 23, 1996), *reprinted at* 142 Cong. Rec. S. 8736, *S8737.

scientists and experts."[46] In this case, the best available science supports the determination that a 20 ppb tolerance is safe.

The tolerance for procymidone illustrates the importance EPA attaches to evaluating actual exposure when determining safety of a pesticide residue. Before passage of the FQPA, EPA had established an interim tolerance for procymidone based on a careful assessment of the toxicological and exposure data, which satisfied the Agency that the risk was "low." In 1990, residues of the fungicide procymidone were discovered in shipments of wine imported into the United States from Europe. Procymidone was not used on grapes in the United States and was not registered under the FIFRA. Moreover, no tolerance had been issued for procymidone residues under the FDCA, and the presence of any such residues rendered the imported wines adulterated. Acting on a petition submitted by the manufacturer of procymidone, EPA established an interim four-year tolerance for raw wine grapes and subsequently established a permanent tolerance.

In so doing, EPA examined the toxicity, carcinogenicity, and mutagenicity of procymidone as well as the levels consumers might be expected to ingest. It concluded:

> Both EPA scientists and the Scientific Advisory Panel agreed that the risk posed by procymidone was low. EPA's conclusion in this final rule is that the risk posed by procymidone is so slight that the proposed procymidone tolerance would be protective of public health.[47]

EPA reached this conclusion despite the facts that procymidone residues (i) posed a quantifiable carcinogenic risk; (ii) were believed to affect reproductive organs and functions, and (iii) posed a quantifiable risk of developmental toxicity.

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46 H.R. Rep. 2284, at 826.

47 56 Fed. Reg. 19518, 19519 (April 26, 1991).

In its risk assessment, EPA emphasized that the potential for consumer exposure to, and thus the health risk from, procymidone were limited by two factors that are equally applicable to possible Cry9C protein exposures. The first was that consumers did not confront other exposures to procymidone because the interim tolerance was the first authorization for the presence of procymidone.[48] Second, in establishing the first tolerance, EPA noted the procymidone residues were dramatically reduced by processing of the grapes. The Agency therefore focused on the anticipated rather than a theoretical worst case exposure in reporting its risk assessment:

> Since imported wine grapes will not be directly consumed, and study data indicate that residues of procymidone are significantly reduced upon processing to wine, use of the tolerance level of 5.0 ppm [in the risk assessment] would have produced unrealistic estimates. Therefore, a typical, or anticipated, residue level of 2.4 ppm supported by the field trial data on wine grapes was used to estimate dietary risks. . . .
>
> EPA routinely performs chronic and cancer risk estimates using anticipated residues since tolerance levels do not reflect actual or typical residue levels found in foods. Averaging of residue levels (here, an average from field trials using maximum application rates) is appropriate for estimating chronic risks because with chronic risks, EPA is concerned with exposure over a person's lifetime. Over a lifetime, exposure will likely be an average of the range of residue values, not the high end residue value. Moreover, averages are particularly appropriate where the food through which most exposure will occur (here, wine) results from the blending of the commodity.[49]

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48 *Id*.

49 59 Fed. Reg. 42511, 42512 (August 18, 1994). The field trials referred to were tests in which procymidone was applied to grapes which were then made into wine. *Id*. at 42513.

Finally, in expediting action on the interim tolerance, EPA also took into account the economic and trade disruptions that could be caused by the absence of a tolerance.[50]

Since enactment of the FQPA, EPA has continued to establish finite tolerances under section 408 for carcinogenic substances where exposures will be low.

F. The Proposed Tolerance Is Consistent with Section 408's Analytical Method Requirements

Under section 408, EPA may not establish a tolerance unless there is a "practical method for detecting and measuring the levels of the pesticide chemical residue in or on the food."[51] A tolerance cannot be established if there is no way to determine whether the tolerance has been met. The lateral flow strip test permits detection in raw commodities and in processed foods. Because it can readily be used in the field, selection of the strip test will facilitate compliance with required testing and accuracy of test results. This in turn will protect the food supply by ensuring that Cry9C protein is more likely to be detected by grain handlers and diverted to feed or non-food industrial uses before entering the human food supply.

G. FDA and EPA Both Have Established Tolerances Keyed to Mandatory Screening of Foods or Food Ingredients

A 20 ppb tolerance for Cry9C protein that is conditioned upon prescribed inbound screening of raw corn at the mill also is consistent with the prior practice of basing safety determinations and tolerances on the use of specified screening or detection levels. A tolerance conditioned on screening of the raw commodity also is consistent with the pass-through provision of section 408 which requires the use of good manufacturing practices to assure

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50 56 Fed Reg. at 19519.

51 Section 408(b)(3)(A) of the FDCA.

removal of Cry9C protein residues to the extent reasonably possible. FDA currently recommends that dry millers screen incoming raw commodities for Cry9C protein residues.[52]

Sulfites. In 1985, FDA determined that recent scientific developments had shown that sulfites "produce allergic-type responses in humans, and the presence of these ingredients in food may have serious health implications for those persons who are intolerant of sulfites."[53] FDA treated sulfites as a no-threshold substance because no threshold had been experimentally demonstrated: "the agency believes that the available information is inconclusive regarding whether there is a biological threshold level for sulfiting agents below which sensitive individuals will not experience adverse reactions."[54]

Based on available data, FDA amended its regulations to provide that sulfiting agents no longer would be considered Generally Recognized as Safe ("GRAS") if used on fruits and vegetables intended to be served raw.[55] The use of sulfites on grapes was not included in FDA's action because sulfites were used on grapes as a fungicide. This use was within the jurisdiction of EPA rather than FDA.[56]

In response to FDA's revocation of GRAS status for sulfites, EPA announced an interim policy allowing the marketing of grapes treated with sulfites, provided that shippers

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52 *See* FDA recommendations for sampling and testing yellow corn and dry-milled yellow corn shipments intended for human food use for Cry9C protein residues, *available at* http://vm.cfsan.fda.gov/~dms/starguid.html.

53 50 Fed. Reg. 13306, 13306 (April 3, 1985).

54 51 Fed. Reg. 25012, 25014 (July 9, 1986). *See also* 50 Fed. Reg. at 13307 ("FDA is unaware of any evidence that establishes a level below which these substances will not cause a reaction in sensitive individuals.").

55 51 Fed. Reg. 25021 (July 9, 1986).

56 51 Fed Reg. at 25024.

could certify that their grapes contained no detectable residues of sulfur dioxide when tested by a particular method, which was capable of detecting sulfite residues at 10 parts per million (ppm), a level that is orders of magnitude higher than the 20 ppb proposed by Aventis.[57]

In January 1989, EPA issued a proposed rule establishing a tolerance at 10 ppm for sulfur dioxide on grapes.[58] In so doing, EPA recognized that permitting sulfites below 10 ppm posed a minimal, insignificant risk. In its final rule establishing a 10 ppm tolerance for sulfite residues on grapes in May 1989,[59] EPA included that the 10 ppm tolerance would "protect the public health."[60] This tolerance did not require certification, tagging, or placarding, and did not require that growers or shippers attempt to notify sulfite-sensitive individuals that grapes had been treated with sulfur dioxide and therefore could bear residues below 10 ppm.

Separately, FDA issued regulations on disclosure of the presence of sulfites in foods. The agency expressly rejected a "biological criterion" for sulfite labeling and selected an "analytical capability" instead.[61] In the final rule, FDA required labeling for sulfite content only if it exceeded the 10 ppm threshold of detection. FDA went on to expressly reject the suggestion that this threshold should be reduced as more sensitive analytical methods were developed:

> Some comments expressed concern that if sulfite labeling is based on the limit of detection for sulfite, then the trigger level will be lowered as the detection is lowered.
>
> The agency is aware that much work is currently being done to lower the analytical detection limit for sulfites and to improve specificity. However, FDA wishes to reassure interested

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57 51 Fed. Reg. 47240 (December 31, 1986).

58 54 Fed. Reg. 384 (January 5, 1989).

59 54 Fed. Reg. 20125 (May 10, 1989).

60 54 Fed. Reg. at 20126.

61 51 Fed. Reg. at 25014.

> persons that it does not have plans to change the definition of a significant amount of sulfite based solely on improvements in methodology, unless justified by new data on the health consequences of sulfites in processed foods.[62]

In fact, FDA has not changed its sulfite labeling rule to incorporate more sensitive analytical methods developed since it promulgated the final rule in 1986.

Aflatoxin. FDA's enforcement policy for aflatoxin, a naturally occurring and thus unavoidable mold contaminating food is likewise predicated on the use of methods of analysis accepted by the Association of Official Analytical Chemists.[63] This action level specified the level of aflatoxin -- 20 ppb -- that could be present in food without risking FDA enforcement action; for practical purposes, it was the equivalent of a determination that aflatoxin below the specified level was safe for human consumption. In setting the action level, FDA took into account the fact that grain milling and food processing dramatically reduce aflatoxin residues, as they do Cry9C residues:

> Studies show that two general methods for processing corn -- dry and wet milling -- remove a major portion of any aflatoxin which may have been present initially. For example, corn starch derived from wet milling has been found to have only 1 percent of the aflatoxin present in the raw corn.
>
> Heat processing and cooking also reduce any remaining aflatoxin.[64]

FDA's Compliance Policy Guide established the "action level" for aflatoxin of 20 ppb on human foods beginning in 1969. Even though a more sensitive test method later became

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62 *Id*.

63 *See, e.g.,* FDA, Compliance Policy Guide 555.400.

64 FDA Talk Paper T89-21 (April 13, 1989).

available, FDA did not reduce the 20 ppb action level for other foods to incorporate the new test methods.

Animal Drug Residues. FDA's "sensitivity of method" policy for regulating carcinogenic veterinary drugs also relies on a prescribed detection method. Under section 512(d)(1)(I) of the FDCA, a carcinogenic drug may be administered to food-producing animals provided that no residue of the drug can be detected by a method of detection prescribed by FDA. FDA has employed a risk assessment analysis to determine the level of detection such a method must achieve.[65] FDA explained its rationale as follows:

> FDA has been unable to conclude that no trace of any given substance will remain in animal products. The new procedures, therefore, provide an operational definition of "no residue." That is, the procedures are designed to permit the determination of the concentration of residue of a carcinogenic compound that presents an insignificant risk of cancer to the consuming public. That concentration corresponds to a maximum lifetime risk of cancer to the test animal on the order of 1 in 1 million. Thus, the procedures provide for a quantitative estimation of the risk of cancer presented by the residues of a carcinogenic compound proposed for use in food-producing animals. "No residue" remains in food products when conditions of use. . .ensure that the concentration of the residue of carcinogenic concern in the total diet of people will not exceed the concentration that has been determined to present an insignificant risk. . . .
>
> Further, before FDA will approve the compound, an analytical method must be available that can accurately and dependably measure the carcinogenic residues of the compound at a concentration corresponding to that estimated to result in an insignificant potential risk to humans.[66]

FDA continues to use the sensitivity of method regulation today.

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65 The implementing regulations appear at 21 CFR 500.80 through 500.92.

66 52 Fed. Reg. 49571, 49572 (December 31, 1987).

H. EPA Has Authority to Establish a Tolerance for Cry9C Protein Even Though StarLink Was Not Approved for Human Food

EPA has explicitly acknowledged that it has authority to establish a tolerance for a pesticide (or implicitly, for a use) that has not been registered under FIFRA. In establishing a tolerance for procymidone, which was not registered for use in the United States, EPA flatly rejected the argument that it had no authority to set a permissible level for an unregistered pesticide: "A tolerance may be established for a pesticide not registered under FIFRA."[67] The situation in which a pesticide is not registered for a particular use (in this case, a human food use) is no different. In this case, the tolerance is designed to address consequences of a legal use (animal feed) that were not foreseen by Aventis or by EPA at the time of the split registration or the renewals thereof. Aventis is not asking EPA to legalize via a tolerance an unlawful use by Aventis.

In 1995, EPA issued a time limited tolerance for the pesticide chlorpyrifos in or on raw oats used for animal feed.[68] A pest control operator under contract to General Mills had improperly treated stored oats with chlorpyrifos, which was not registered for use on oats, and fraudulently claimed to have used a different pesticide. EPA noted that it generally does not grant a tolerance to cover misuse; however, EPA granted the chlorpyrifos tolerance on the grounds that: (1) the pesticide residue did not pose a health hazard; (2) the petitioner was not directly responsible for the misuse, and (3) if the tolerance were not approved, large quantities of oats would have to be destroyed.

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67 56 Fed. Reg. 19518, 19518 (April 26, 1991).

68 60 Fed. Reg. 7509 (February 8, 1995); 60 Fed. Reg. 15488 (March 25, 1995). General Mills withdrew the petition for a time-limited tolerance on finished food products in light of an upcoming "ship by" date used to ensure product freshness.

These factors apply with equal or greater force to the tolerance sought in this petition. The possible presence of Cry9C protein in food is not a result of any misuse. Rather, it is the unavoidable and unforeseeable consequence of the combination of the split registration granted by EPA, and other factors beyond the control of Aventis. In addition, as shown in this petition, there is no health risk posed by possible levels of Cry9C protein in food and, in the absence of a tolerance, there could be major disruptions in the food supply and export markets.

I. The Data Provided With this Submission Supports a Determination That a 20 ppb Tolerance Satisfies the Reasonable Certainty of No Harm Standard Under the FQPA

The FQPA directs EPA to consider several factors when establishing a tolerance. The factors relevant to this petition are listed below, together with the responsive data provided with this petition.

> *(i) The validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue.*
>
> Aventis has provided extensive data concerning the characteristics of Cry9C protein.
>
> *(ii) The nature of any toxic effect shown to be caused by the pesticide chemical or pesticide chemical residue in such studies.*
>
> No data have yet confirmed that Cry9C protein is a human allergen or has any other toxic effect.
>
> *(iii) Available information concerning the relationship of the results of such studies to human risk.*
>
> No data have shown Cry9C to be an allergen or toxin. Therefore no extrapolation concerning its possible effects on humans is necessary or possible.
>
> *(iv) Available information concerning the dietary consumption patterns of consumers (and major identifiable subgroups of consumers).*
>
> This information is provided by the updated exposure assessment.

(v) Available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity.

Cry9C protein has not been shown to be a human allergen or toxin; moreover, there is no evidence that consumers are exposed to any other substances that might be similar in effect. Therefore, this factor does not apply.

(vi) Available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue and exposure from other non-occupational sources.

Dietary exposure is the only potential source of human Cry9C protein exposure. It is not in water, nor in household use, nor encountered in the workplace. There are no other tolerances in effect for Cry9C protein.

(vii) Available information concerning the variability of the sensitivities of major identifiable subgroups of consumers.

Cry9C protein has not been shown to be an allergen. The potential human dietary exposure of consumer subpopulations has been evaluated in the updated exposure reports. No subpopulation has an exposure that is greater than the U.S. population at large.

The FQPA also authorizes EPA to rely on reliable information about actual exposures rather than the highly conservative assumptions it had historically incorporated in risk assessments. EPA may rely on data concerning the percentage of food actually treated with a pesticide and the data concerning the "actual residue levels of the pesticide chemical that have been measured in food."[69] The FQPA thus specifically authorizes EPA to rely on data concerning the actual use of pesticides and actual residue levels in order to arrive at a more accurate estimate of potential for human exposure to pesticide residues. EPA's own study of

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[69] Section 408(2)(E) and (F) of the FDCA.

wet milling shows that Cry9C protein residues are virtually eliminated by that process and Aventis' own study (Volume 5) demonstrates that processing of dry milled corn reduces Cry9C protein in finished food by 80 to 99.9 percent.

The data provided by Aventis with this petition demonstrate that the potential for human dietary exposure to Cry9C is currently negligible and expected to decrease. Coupled with the absence of any scientific data indicating that Cry9C protein is an allergen, this minute potential for exposure supports the conclusion that a tolerance for Cry9C protein at 20 ppb is well within the reasonable certainty of no harm standard.

VII. CONCLUSION

The reports accompanying this proposal tell us three things. First, that inbound testing at the dry mills ensures that Cry9C protein at concentrations exceeding 20 ppb is being redirected to approved animal feed and non-food industrial uses. The existing corn containment efforts, including the mandatory use of strip tests that Aventis now proposes, will provide additional assurance. Second, Cry9C protein in dry-milled raw corn is reduced by 80 to 99.9% by processing; it is substantially reduced in all cases and virtually eliminated in the majority of corn-containing processed foods. Third, based on these findings, the updated exposure assessment concludes that the highest consumers of corn-containing foods potentially would consume only 0.37 micrograms of Cry9C protein per day, 95% of the U.S. population would consume no more than 0.1 microgram per day and three-quarters of the U.S. population would consume no measurable amount or none at all.

An enforceable tolerance of 20 ppb for Cry9C protein in raw corn will assure that, after processing, no more than miniscule residues will occur in finished food. Such levels in finished food present a negligible risk to human health. The history and application of the "reasonable certainty of no harm" standard demonstrates that, for nonthreshold substances, a finding of "insignificant risk" has been treated by EPA and FDA as safe for the purposes of human health.

The measures taken by Aventis, growers, grain handlers, millers, and USDA already have limited potential consumer exposure to Cry9C protein. Coupled with these measures, the proposed tolerance and required screening will ensure that any possible consumer exposure to Cry9C protein is at an extremely low and safe level. Only those food products with levels of Cry9C protein that exceed the 20 ppb level would be considered legally adulterated. This will eliminate the current uncertainty with respect to the legal status of processed foods and the potential for recalls of foods that present no significant health risk to consumers.

The presence of Cry9C protein in the human food supply already has caused substantial disruption in the corn industry among growers, grain handlers, millers, food processors, and exporters. Aventis and these other stockholders have taken great strides to reduce the level of Cry9C protein in the human food supply. These efforts have not been and cannot be 100% effective. Prompt action on this petition is now needed, not only to avoid more economic disruption, but also to restore consumer confidence in the food supply.

Given the significance and urgency of this matter both in the United States and abroad, we encourage EPA to act promptly on this petition.

ENVIRONMENTAL PROTECTION AGENCY

[PG- ; FRL-]

Aventis CropScience, Pesticide Tolerance Petition

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of Filing

SUMMARY: This notice announces the initial filing of a pesticide petition proposing the establishment of a conditional tolerance for residues at a level of 20 ppb of *Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein in or on the raw agricultural commodity, corn. The proposed tolerance is conditional upon the mandatory testing of raw corn entering dry milling operations for the production of human food. The testing is to be accomplished by the use of a validated Lateral Flow Strip Test with a limit of detection of 20 ppb Cry9C protein. Corn containing more than 20 ppb Cry9C protein will continue to be directed to animal feed and non-food industrial uses. The summary of the petition published in this notice was proposed by the petitioner.

DATES: Comments, identified by the docket number [PF-], must be received on or before, (insert date 30 days after date of publication in Federal Register).

ADDRESSES: By mail, submit written comments to Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St. SW., Washington, DC 20460. In person, bring comments to RM 1132, CM#2, 1921 Jefferson Davis Highway, Arlington, VA 22202.

Comments and data may also be submitted electronically by sending electronic (e-mail) to: opp-docket@epamail.epa.gov. Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comments on data will

also be accepted on disks in WordPerfect 5.1 file format or ASCII file format. All comments and data in electronic format must be identified by docket number [PF-]. Electronic comments on this notice may be filed online at many Federal Depository Libraries. Additional information on electronic submission can be found below in this document.

Information submitted as comments concerning this document may be claimed confidential by marking any part or all of that information as "Confidential Business Information" (CBI). CBI should not be submitted through e-mail. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments will be available for public inspection in Rm. 1132 at the address given above, from 8 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT; By mail: Regulatory Action Leader Name (BPPD to provide), (RM 90), Biopesticides and Pollution Prevention Division, office of Pesticide Programs, U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460. Office location and telephone number: 5th floor CS#1, 2800 Crystal Drive, Arlington, VA 22202, Telephone No. 703-308 - ____, e-mail: last name, firstname@epamail.epa.gov.

SUPPLEMENTARY INFORMATION: EPA has received a petition (PPXXXXX) from Aventis CropScience, 2 TW Alexander Drive, Research Triangle Park, NC 27709, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. section 246s(d), to amend 40 CFR part 1890 by establishing a conditional tolerance for residues at a level of 20 ppb of *Bacillus thuringiensis* subsp. *tolworthi* Cry9C protein in or on the raw agricultural commodity, corn. The proposed tolerance is conditional upon the mandatory

testing of raw corn entering dry milling operations for the production of human food. The testing is to be accomplished by the use of a validated Lateral Flow Strip Test with a limit of detection of 20 ppb Cry9C protein. Corn containing more than 20 ppb Cry9C protein will continue to be directed to animal feed and non-food industrial uses.

Pursuant to section 408(d)(2)(A)(i) of the FFDCA, as amended, Aventis CropScience has submitted the following summary of information, data and arguments in support of its pesticide petition. This summary was prepared by Aventis CropScience and EPA has not fully evaluated the merits of the petition. The summary may have been edited by the EPA if the terminology used was unclear, the summary contained extraneous material, or the summary was not clear that it reflected the conclusion of the petitioner and not necessarily EPA.

VIII. SUMMARY OF PETITIONS

A. Product Name and Previous Use Practices

StarLink corn contained the insect control protein named Cry9C, which is derived from the common soil bacterium, *Bacillus thuringiensis* subsp. *tolworthi*. Aventis voluntarily cancelled the registration for StarLink corn. However, StarLink corn grain grown in previous growing seasons and other corn containing Cry9C protein may continue to be used for animal feed or non-food industrial uses in accordance with the existing exemption from the requirement for a tolerance for these uses.

B. Product Identity/Chemistry

1. Identity of the Pesticide and Corresponding Residues.

The *cry9C* gene was isolated from the *B.t. tolworthi* strain, truncated, and modified before it was stably inserted into corn plants. The tryptic core of the microbially produced Cry9C delta-endotoxin is similar to the Cry9C protein found in event CBH-351. The

Cry9C protein was produced and purified from a bacterial host, for the purposes of mammalian toxicity studies.

2. Recommended Method of Analysis

The proposed enforcement method for use on raw corn destined for dry milling is the EnviroLogix or Strategic Diagnostics Inc. Lateral Flow Strip Test, both of which have been validated by USDA GIPSA and Aventis. The limit of detection for these two tests is 20 ppb Cry9C protein. The method must be used in accordance with the recommended sampling methods (FDA Recommendations for Sampling and Testing Yellow Corn and Dry-milled Yellow Corn Shipments Intended for Human Food Use for Cry9C Protein Residues, FDA-CFSAN, January 19, 2001).

C. Mammalian Toxicological Profile

Aventis has conducted an extensive array of toxicological testing including oral and intravenous administration, as well as acute and short-term exposure. EPA has reviewed these data and concluded that there is no toxicological endpoint of concern, with the possible exception of allergencity.

The gene for the Cry9C protein comes from a non-allergenic common soil bacterium, *Bacillus thuringiensis*. The corn plant, into which the gene for the Cry9C protein was inserted, is rarely allergenic to humans. Expression of the gene for the Cry9C protein did not enhance the potential of corn to be allergenic, as demonstrated by the absence of any difference in reactivity to StarLink corn than to wild type non-transgenic corn in radioallergosorbent tests (RAST) performed with human sera from corn allergic patients (MRID Number 443844-05).

The Cry9C protein was not toxic upon single oral or repeated dietary administration to rats and has no linear amino acid sequence homology to any known human allergen or toxin (Oral LD50 > 3,760 mg/kg/day, MRID Number 442581-07; Acute intravenous

LD50 > 0.3 mg/kg/day (MRID Number 447343-02); 30-day repeated dose toxicity test in rats: up to 328 mg/kg/day produced no adverse effects, no binding to villi or enterocytes lining GI tract crypts of both large and small intestines, MRID Number 447343-03; MRID Numbers 443844-04, 442581-09). RAST tests performed with sera from individuals allergic to the well-known human food allergens, wheat; rice; buckwheat; soy; peanut; milk; eggs; and shrimp confirmed that even individuals with pre-existing food allergies demonstrated no cross-reactivity to Cry9C (MRID Number 452464-01). The level of the Cry9C protein in whole corn grain, 0.0129%, is a very low level of total protein expression in the plant compared to most allergens which are present at 1-40% of the total plant protein (MRID Number 450257-01).

The Cry9C protein is somewhat more stable than the other *Bt* Cry proteins already approved for food use. Cry9C does digest in simulated stomach fluids at pH of 1.2-1.5 within 30 - 60 minutes (within normal stomach emptying time) and does denature at temperatures likely to be encountered during cooking and processing (MRID Numbers 44734305, 44258108, 45114401, 445114402). Although Aventis interprets these data to mean that Cry9C protein is not an allergen, regulatory officials have not been able to confirm this assessment.

D. Residue Profile

Aventis developed an analytical method to determine Cry9C protein levels in intermediate and finished food products. Studies were conducted to assess the level of Cry9C protein typically found in 12 representative food products made from 100% StarLink corn. These studies demonstrate that there is significant reduction (80-99.9%) of Cry9C protein levels, relative to levels found in raw corn, during the manufacture of food products. Three processing factors are responsible for destruction of Cry9C protein: heat, shear or pressure, and alkali treatment.

E. Aggregate Exposure

1. Dietary Exposure

Aventis has performed a new dietary risk assessment. Worst case estimates of potential dietary intake of Cry9C protein were calculated using Novigen Sciences, Inc., Food and Residue Evaluation Program (FARE™) software, food consumption data in the 1994-1996 USDA's Continuing Survey of Food Intakes by Individuals (CSFII), and the new Aventis study on reduction in Cry9C protein levels resulting from food processing. In essence, dietary intake of Cry9C protein was calculated as the product of consumption of corn protein-containing foods and the expected concentration of Cry9C protein in such foods. Intakes were estimated on a "per consumer" basis for the overall US population, children 1 to 6 years of age, children 7 to 12 years of age, the Hispanic population in the US, Hispanic children 1 to 6 years of age, and Hispanic children 7 to 12 years of age.

2. Non-food Exposure.

Since the Cy9C protein is expressed in plant tissues at very low levels, and since the StarLink product will no longer be used, exposure will be negligible to non-existent via all non-food routes.

F. Cumulative Exposure

Common modes of toxicity are not relevant to the consideration of the cumulative exposure to Cry9C protein.

G. Safety Determination

1. Exposure Assessment

As already discussed, the only relevant safety issue is potential allergenicity via dietary (food) exposure.

a) US Population

Dietary exposure will be the major route of exposure to the U.S. population. Estimated potential daily exposures for all subpopulations at the 99th percentile are below 0.37 microgram per day, the exposure for the general population. The US population in general had the highest estimated daily intake of all subpopulations examined. This newly refined dietary intake estimate of the Cry9C protein is 67 times lower than the EPA's November 2000 upper bound estimate for the US population (25 micrograms per day, 99th percentile), and 10 times below the highest estimate from the Aventis November 2000 estimate (3.9 micrograms per day for the Hispanic population, 99th percentile). Such exceedingly low levels of exposure, coupled with insufficient information to conclude whether or not Cry9C protein is actually a human food allergen, further support the SAP finding that the levels of Cry9C protein present in the human diet are insufficient to either sensitize or cause an allergic reaction. Therefore, the data support a finding of reasonable certainty of no harm and justify a tolerance at 20 ppb.

b) Infants and children

As with the rest of the population, the primary route of exposure is dietary. The dietary exposure assessment indicates that children have less exposure than the general US population. Accordingly, there is no need to apply an additional safety factor for infants and children.

c) Endocrine effects.

EPA's review of the submitted data concluded that there is no toxicological endpoint of concern, with the possible exception of allergenicity.

H. Existing Tolerances/Exemptions

On May 22, 1998, EPA established an exemption from the requirement of a tolerance for residues of Cry9C protein and the genetic material necessary for its production in

corn for feed use only; as well as in meat, poultry, milk or eggs resulting from animals fed such feed. This exemption remains in effect.

I. International Tolerances

To date, no Codex, Canadian or Mexican tolerances exist for *Bt* subsp. *tolworthi* Cry9C protein in corn.

J. Conclusions

Aventis CropScience believes that this petition provides adequate grounds for the establishment of a tolerance of 20 ppb for residues of the insecticide, *Bt* subsp. *tolworthi* Cry9C protein in or on the raw agricultural commodity, corn.